REMARKS

I. Introduction

Upon entry of the present amendment, claims 1-2, 5-6, 8-12, 14-16, 18-24 will be pending in this application. Claims 1 and 6 have been amended to more fully define the invention. Support for these amendments appears in originally presented claim 3 and in the specification at page 3. New claims 18- 24 have been added to more fully define the invention. Support for new claims 18-21 appears in the specification at page 5. New claims 22-24 correspond to original claims 5, 9, and 12, but depend from claim 6 rather than claim 1. A revised Figure 2 has also been submitted. No new matter has been added.

II. Drawings

In the Office Action mailed January 22, 2003, the Examiner objected to the key in Figure 2, asserting that the key does not explain the drawing. Applicants submit new Figure 2 as a corrected drawing. The shading has been added to clarify the key and the corresponding regions of the strands.

III. 35 U.S.C. § 102(b)

The Examiner rejected claim 13 as being anticipated by Vary (WO 92/11390). Without conceding to the Examiner's rejection but in the interest of advancing the prosecution of this case, applicants have cancelled claim 13, rendering this rejection moot. Accordingly, Applicants respectfully request that the Examiner withdraw this rejection.

IV. 35 U.S.C. § 103(a)

A. Vary in view of Ecker

The Examiner rejected claims 1, 3-6, 8, 12 under 35 U.S.C. § 103(a) as unpatentable over Vary (WO 92/11390) in view of Ecker (U.S. Patent No. 5,641,625) on the basis that Vary teaches the use of a probe for detection of a nucleic acid sequence target by formation of a triple helix. The Examiner states that the target sequence contains a polypurine region (page 5, lines 20-21) and the probe contains a high polypyrimidine (col. 4, lines 25). The Examiner further asserts that Vary teaches introducing a polypyrimidine on the 5' end of a primer to introduce high polypurine target into amplified DNA (page 30, lines 15-20), and detection on electrophoretic gel (see example 1).

Although the Examiner admits that Vary fails to teach the use of a peptide nucleic acid (PNA), the Examiner cites Ecker as teaching PNA probes which bind with high stability and

specificity to double stranded DNA (col. 4, lines 4-47, col. 15, lines 1-5.) The Examiner's position is that one of ordinary skill in the art would have been motivated to apply the PNA probes described by Ecker to Vary's detection method in order to provide a probe that binds specifically to a target sequence. Applicants respectfully traverse this rejection and request reconsideration and withdrawal thereof.

Without conceding to the Examiner's rejection but in the interest of advancing the prosecution of this case, applicants have amended claims 1 and 6 to clarify that the contacting step (b) is conducted **during** the amplifying step (a). In other words, the PNA probes are used **during** the amplification reaction. Applicants respectfully submit that there is no teaching or suggestion of this feature by either Vary or Ecker.

Ecker teaches that PNA probes bind with high stability and specificity to double stranded DNA. The stability with which they bind is so great that they are able to modify protein activity. One skilled in the art would be unable to predict with any certainty how the presence of such probes during an amplification would affect the reaction. High stability binding such as described by Ecker is also described in the Kamenetski reference (Frank-Kamenetski, WO 97/14793) cited by the Examiner. Kamenetski teaches the use of PNA sequences as nucleic acid clamps for various uses including the inhibition of background signals (see page 17, lines 14-27 of Kamenetski). Kamenetski states that, once a PNA probe has bound to a sequence, it "inhibits further rounds of PCR amplification." Accordingly, one of ordinary skill in the art reading the Kamenetski paper would **avoid** the use of PNA probes during an amplification reaction because one would expect that the stability of the triplex would **significantly inhibit** amplification. Therefore, Kamenetski and Ecker actually teach away from the claimed detection method.

Applicants unexpectedly discovered that the use of PNA probes during amplification fails to inhibit amplification. Others have followed the teachings set forth by applicants in the present application and obtained successful results such as described in the scientific paper of Wolffs *et al.* entitled, PNA-Based Light-Up Probes for Real-Time Detection of Sequence-Specific PCR Products, *Biotechniques* 31:766-771 (2001), a copy of which is attached as Attachment A.

Accordingly, Applicants respectfully request that the Examiner withdraw this rejection.

B. Vary in view of Ecker in further view of Wang

The Examiner rejected claims 9-11, 15, and 16 under 35 U.S.C. § 103(a) as unpatentable over Vary (WO 92/11390) in view of Ecker (U.S. Patent No. 5,641,625), and further in view of

Wang (*J. Am Chem. Soc.* 119: 7667-70, 1996) on the basis that Wang teaches a biosensor attached to PNA probes for detection. The Examiner states that one of ordinary skill in the art would have been motivated to apply the Wang biosensor PNA surface probes to the combination of Vary and Ecker in order to increase the high throughput and sensitivity of detection. Applicants respectfully traverse this rejection and request reconsideration and withdrawal thereof.

The biosensor used by Wang is a electrochemical detector, which carries out chronopotentiometric measurements to detect hybridization electrochemically. Wang describes PNA probes as being useful in this type of detection system because of their electrochemical properties. However, Wang fails to teach the use of a surface plasmon resonance detector.

As applicants have described in Example 2 of the present application, the use of a surface plasmon resonance detector provides unique advantages. For example, the target can be detected in near real time, as shown in Figure 3. This finding has subsequently been illustrated by those skilled in the art such as Feriotto *et al.*, as described in their scientific paper entitled, Peptide Nucleic Acids and Biosensor Technology for Real-Time Detection of the Cystic Fibrosis W1282X Mutation by Surface Plasmon Resonance, *Laboratory Investigation* 81:1415-1427 (2001), a copy of which is enclosed as Attachment B. Although unexpected, Feriotto *et al.* clearly demonstrate the efficacy achieved when PNA was combined with surface plasmon resonance as taught in the present application. Therefore, the superiority of the claimed detection system, such as for producing real-time detection, have now been appreciated by those skilled in the art. Accordingly, Applicants respectfully request that the Examiner withdraw this rejection.

C. Vary in view of Frank-Kamenetski

The Examiner has also rejected claims 1-6, 8, 13, and 14 under 35 U.S.C. § 103(a) as unpatentable over Vary (WO 92/11390) in view of Frank-Kamenetski (WO 97/14793) on the basis that Frank-Kamenetski teaches a bis-PNA for binding to double-stranded DNA, that the PNA clamps show high stability, and that they may be used in PCR to avoid competing side reactions such as amplification of non-target sequences in background and primer oligomerization. The Examiner's position is that one of ordinary skill in the art would have been motivated to apply Frank-Kamenetski's probes to Vary's detection method to provide a probe that binds specifically to a target sequence. Applicants respectfully traverse this rejection and request reconsideration and withdrawal thereof.

As mentioned above, the Vary reference and the Frank-Kamenetski reference are not properly combinable. Frank-Kamenetski is directed to nucleic acid clamps that are intended to inhibit or prevent amplification, selectively cleave nucleic acids, or to regulate gene expression in the treatment of disorders. The clamp may be hybridized to a target nucleic acid at a binding site to form a triple helix and the triple helix inhibits interaction between the nucleic acid and the protein. There is no suggestion to use the clamp to detect the presence of a product. On the other hand, the Vary reference is primarily directed to sequence detection. The references relate to different areas of endeavor, and one of ordinary skill in the art would not be motivated to combine the references together

Furthermore, even if the references were properly combinable, their combination does not teach every element of Applicants' claimed invention. The Frank-Kamenetski reference refers to nucleic acid clamps that can be used on PCR. See page 17, line 14-27. This concept teaches away from conducting Applicants' amplifying and contacting steps simultaneously. Accordingly, applicants respectfully request that this rejection be withdrawn.

D. Submission of Newly Added Claims

Applicants have added new claims 18-21, which specify that the sample is contacted with a wave guide of an evanescent wave guide detector on which is immobilized a peptide nucleic acid. Support for these new claims can be found on page 5 of the present application. Applicants respectfully submit that the newly added claims are non-obvious in view of the cited references.

CONCLUSION

For at least the above reasons, Applicant respectfully requests allowance of claims 1-2, 5-6, 8-12, 14-16, 18-24 and issuance of a patent containing these claims in due course. If there remain any additional issues to be addressed, the Examiner is invited to contact the undersigned attorney at 404-745-2473.